REMARKS

1. Objections

1.1. Claims 134-137 were objected to for depending from claim 1, drawn to a glycolipopeptide, but reciting "method of claim 1". We have replaced "method" with "glycolipopeptide".

1.2. Claims 8, 11, 13, 47, 48, 87 and 89 were objected to for failing to further limit the subject matter of their base claims.

The Examiner mistakenly assumes that claims 8, 11 and 13 require that the glycolipopeptide comprise a single MUC1 peptide epitope, in conflict with base claim 1. The correct interpretation is that they simply impose an additional limitation on at least one of the two epitopes of claim 1.

8 further limits base claim 1 because claim 1 would cover presentation of two epitopes comprising a particular sequence neither of which need be T-cell epitopes, whereas 8 requires that at least one of the epitopes be a T-cell epitope. In this regard, note that PDTRP by itself is generally considered to be only a B-cell epitope, whereas SAPDTRP is both a T-cell and B-cell epitope, see P59, L24-26.

11 further limits the sequence P(D/E)(A/G/T/S) (R/K/H)P of base claim 1 to PDTRP.

13 further limits base claim 1 by requiring that it comprise SEQ ID NO:10. Claim 1 only requires a sequence reading on AAs 6-10 of SEQ ID NO:10, hence 13 is imposing the requirement of AAs 1-5 and 11-20 of SID 10 in appropriate structural relationship to PDTRP (and of course PDTRP is only one embodiment of the generic pentapeptide of claim 1, as discussed already vis-a-vis claim 11. Claim 1 would read upon the peptide PDTRPPDTRP (with appropriate glycosylation and lipidation) whereas claim 13 would not.

Claims 47 and 48 are said to be in conflict with the requirement of base claim 1 that an interior amino acid be lipidated. However, nothing in claim 1 forbids that a terminal amino acid also be lipidated, nor do claims 47 and 48 require that no interior amino acid be lipidated and thereby contradict claim 1.

Claims 87 and 89 duplicated 11 and 13, respectively. They have been amended to require at least two copies of PDTRP and SAPDTRP, respectively. They further limit claim 1 for the reasons explained vis-a-vis 11 and 13.

2. Election/Restriction

2.1. We appreciate that the request to rejoin the method claims of group II cannot be granted until the prerequisite set forth in MPEP 821.04 is satisfied, i.e., a product claim of group I is deemed patentable over the prior art and the method claims are dependent on such product claim. However, we don't wish the possibility of rejoinder to be overlooked.

2.2. Claims 134-137 should be rejoined in view of the amendment explained in section 1.

3. Definiteness (OA pp. 6-7)

3.1. The examiner questions "where at least one epitope is a cancer-associated epitope other than a MUC1 peptide epitope" (claim 2). The claim has been amended to read, "The glycopeptide of claim 1 which further comprises at least one cancer-associated epitope other than a MuC1 peptide epitope".

3.2. With respect to claim 8, the T cell epitope isn't the recited MUC1 peptide epitope because PDTRP is just a B-cell epitope. But it could comprise that sequence, e.g., the T cell epitope SAPDTRP, or be overlapping, or be wholly separate. See

P13, L7-14.

3.3. We have corrected the antecedent basis problems for claims 11, 36, 37, 38-46, 70, 72 and 88. Claim 87 is cancelled.

3.4. With respect to claim 62-64, 68 and 69, "analogously" means that the allowed values for A' are the same as for A, the allowed values for Y' are the same as for Y, and the allowed values for Z' are the same as for Z, not that -A'-A, Y'=Y or Z'=Z. This has been made explicit in 62.

3.5. The examiner objects to claims 73 and 74 as it is allegedly unclear whether the amino acid sequence is, as recited, that of SEQ ID NO:2 (with two lipidated serines), given that the claim also says that "Lipids" refers to "two or more consecutive amino acids".

We have changed the definitions of "Lipids" to be "two lipidated serines", so the amino acid sequence is that of SEQ ID NO:2. This in turn rendered claims 139 and 140 redundant, and hence those have been cancelled. However, we have added claims 141-148 which are based on these sequences and related teachings.

4. Written Description

The Examiner questions written description for T cell epitopes other than the disclosed MUC1 T cell epitope, SAPDTRP, and hence for claims 8 and 10. The Examiner argues that finding a T cell epitope is not a trivial matter. However, the teachings of the specification are more than trivial.

We discuss T cell epitopes generally at page 8, lines 6-20, identifying them as linear peptides (8-24 aa) or oligosaccharides. This is elaborated on at pages 41-42.

A Neisseria T cell epitope (SEQ ID NO:1) is identified at P12, L7-10.

Cancer-associated epitopes are discussed at pp. 46-56, and

MUC1 epitopes at pp. 58.

The Examiner concedes that SAPDTRP is a T cell epitope (cp. P59, L25-26). It appears that PGSTAPPAHGVT (SID 6) is also disclosed to be a T cell epitope (P60, L28-P61, L2). We disclose three more T cell epitopes (SID 7-9) at P61, L3-10, and at L10 we allude to the "peptide binding motif for HLA A * 201".

At pp. 67-70, we discuss generic methods of identifying and predicting T cell epitopes, and cite a paper on the HLA-A2 binding motif.

In view of the disclosure of <u>five</u> MUC1 T cell epitopes, the known HLA-A2 binding motif, and the disclosed methods, we believe written description is satisfied.

As evidence of lack of WD, the Examiner cites USP 5,840,839 on the difficulties of finding a HLA-A31-restricted T cell epitope based on the putative HLA-A31 motif.

While the '839 patent issued in 1998, it was based on an application filed in 1996. The instant application has an April 2002 priority, and the Examiner should not infer that the state of the art in T cell epitope identification was the same in 2002 as in 1996.

Secondly, the HLA31 binding motif used by the '839 patent was that of Falk, Immunogenetics, 40, 238-41 (1994). Such motifs are based, of course, on known HLA-31 sequences, and the more such sequences are known (and the more is known as to which sequences are <u>not</u> HLA-31 restricted) the more accurate the motif is. Even if the HLA-31 motif wasn't a good predictor, that wouldn't support any inference against the published HLA-2.1 motif.

Thirdly, the HLA-31 binding motif in question merely required a hydrophobic residue at position 2 and a positively charged residue at the C terminal. Of the peptides tested (SID

17-28), several had a hydrophilic residue at position 2, namely SID 17 (D), SID 26 (Q) and SID 28 (S). Others had neutral (SID 20) residue (G), or weakly hydrophobic (SID 25, A). Two (SID 21, 22) had Cys at position 2, and Cys is somewhat difficult to classify. On the Hopp-Woods scale in which hydrophobic AAs are negative, glycine is 0.0, alanine is -0.5, cysteine is -1, and the most hydrophobic AA is Trp (-3.4). On the Kyte-Doolittle scale, in which hydrophobics are positive, glycine is -0.4, alanine is 1.8, cysteine is 2.5 and the most hydrophobic AA is isoleucine (4.5).

So, of the Table 1 peptides tested only SID 18 (W2, R9), 23 (W2, R9), 24 (I2, R9), and 27 (V2, K9) really satisfied the HLA-A31 motif. Admittedly, these were negative. But this screened only a very small fraction of the putative HLA-31 motif sequence space. Likewise, only a small fraction of the sequence space is covered by Table 2.

If we interpret the HLA-31 sequence space to treat all amino acids with negative Hopp-Woods scores as hydrophobic, then the nonapeptide sequence space is 11 at position 2, 3 (Arg, Lys, His) at position 9, and 20 at the other 7 positions: about 42,240,000,000 sequences.

In any event, our case for WD doesn't rest solely on a known HLA binding motif, let alone just on HLA-A31. We have, after all, disclosed five known T cell epitopes.

5. Prior Art (OA pp. 9-12)

The following prior art rejections are stated:

(1) Claims 1, 8, 10-15, 18, 19, 21, 22-24, 30-35, 49, 51, 70, 87-90 and 138 are rejected as obvious over Livingston (WO97/34921), in view of Zeng (1996) and Karsten (1998),

(2) Claims 1, 49 and 50 are rejected as obvious over the

above, further in view of Boutillon (USP 5,871,746),

(3) Claims 1, 77-80 are rejected as obvious over the rejection #1 art, further in view of Guan (1998).

Claims 2, 36-46 and 72 were examined but not rejected on prior art grounds.

What we are presently claiming is a glycolipopeptide with at least two PDTRP-like MUC1 peptide epitopes, with at least one being glycosylated and at least one other being unglycosylated.

5.1. The Examiner argues

(1) Livingston teaches (e.g. claim 8) a peptide comprising two MUC1 epitopes (and the claim 8 sequence has two copies of PDTRP);

(2) Zeng teaches a lipopeptide vaccine with Pam3 Cys attached to an internal amino acid;

(3) Karsten teaches that antigenicity of the DTR motif of MUC1 is increased by glycosylation with TF or Tn;

and hence

(4) that the claimed glycolipopeptide is prima facie obvious.

First, we respectfully submit that Zeng does not provide motivation to lipidate a MUC1 peptide.

Zeng lipidated a non-MUC1 peptide, specifically a 23-aa influenza peptide presented in a MAP-4 structure. The lipid (Pam3) was attached to a Cys, in turn attached to the side chain of a Lys, in turn somewhat remote from the actual influenza sequence (see Zeng scheme 2 on p. 60).

In contrast, in our Fig. 2, the MUC-1 derived sequence is attached to SSL, and both of the serines are lipidated.

Also, the Zeng article is just about the synthetic chemistry. It is only at page 67, col. 1 that it is asserted that Pam_3Cys increases the immunogenicity of a peptide antigen,

citing reference [21].

That reference [21] (Deres, 1989, **copy enclosed**), describes a lipidated form of the influenza nucleoprotein peptide NP147-158 (R-)[1]. The form of lipidation is a bit peculiar. Imagine a Cys attached to Ser-Ser, and that to the N-terminal of the NP147-158. One palmitoyl group is then attached to the N-terminal of the Cys. Two more palmitoyl groups are attached to C1 and C2 of a propyl linker, whose C3 is attached in turn to the sulfur atom of the Cys. The resulting lipopeptide P3CSS-[NP147-158 (R-)], was recognized by H-2^d or H-2^b-restricted CTL, but Ser-Ser-[NP147-158(R-)] and NP147-158(R-) weren't efficient for priming.

Thus, in Deres, the lipids are attached to the N-terminal AA (Cys), not an interior AA as required by claim 1.

While Zeng's lipid is attached to an internal AA, Zeng doesn't know whether the resulting lipopeptide in fact has T cell activity --that is an unwarranted extrapolation from Deres. Hence, the art would not read Zeng as teaching lipidation of internal amino acid as increasing T-cell activity even against an influenza peptide, let alone a MUC1 peptide.

Secondly, if the person of ordinary skill in the art were motivated by Karsten to glycosylate the DTR motif in the two-PDTRP peptide of Livingston, the motivation would have been to glycosylated both DTR motifs, and not to leave one unglycosylated as required by amended claim 1.

New claim 149 requires that the glycolipopeptide be a linear peptide, that is, a peptide in which no amino acid is linked by a peptide (-NHCO-) bond to the side chain of another amino acid.

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[1] Counsel believes "R-" denotes that an Arginine was deleted, but doesn't know where. The sequence of NP147-158 (R-) is given as TYQRTRALVTG. If interested, consult Deres reference [6].

Basis exists at page 37, lines 6-7, contemplating peptides produced by gene expression, the distinction between side chains and the main chain at page 38, line 10 to page 39, line 2, and the clearly linear structures of Figures 1 and 2.

New claim 150 requires that the lipidated amino acid be one other than Pam3Cys. Pam3Cys is explicitly disclosed at page 12, lines 5-32 and page 15, lines 17-21, and hence can be disclaimed pursuant to MPEP 2173.05(i). Both claims further distinguish Zeng.

5.2. Claims 1, 49 and 50 are rejected as obvious over the foregoing art, further in view of Boutillon. Boutillon is cited merely to show attachment of Pam3Cys to peptides via Ser, and the Examiner argues that it is obvious to use Ser instead of the lys of Zeng. However, this doesn't remedy the deficiencies of Livingston, Zeng and Karsten as applied to amended claim 1.

5.3. Claims 1 and 77-80 are rejected as obvious over the art of the first rejection, further in view of Guan. Guan is said to teach use of liposomes to deliver peptide antigens containing hydrophobic domains. However, Guan does not remedy the deficiencies of Livingston, Zeng and Karsten as applied to amended claim 1. Guan taught one mouse (SP1-020) and three human (BP16, BP24, BP25) non-glycosylated, non-lipidated MUC1 peptides. Of these, BP24 and BP25 contained two copies of PDTRP. Guan also taught the non-glycosylated lipopeptide LCP25, with laurylcysteine attached to the N-terminal of BP25. Since Guan does not teach any glycosylation, Guan does not provide motivation to differentially glycosylate the two PDTRPs as required by claim 1.

6. Miscellaneous

We take this opportunity to note that we have amended claims

73 and 74 to clarify "Tn" and "Sialyl Tn". The abbreviation "a" was used in these claims to denote "alpha" and we decided it was better to spell this out. We also decided to recite N-acetyl neuraminic acid (Neu5Ac) rather than "sialyl", since "sialyl" in the art can refer specifically to Neu5Ac or more generically to N- and O-substituted derivatives of neuraminic acid. We have also corrected "a GalNAc" to --αGalNAc-- at page 99, lines 6-7, with basis at page 49, line 15. We also have made explicit the -O- linkages to the amino acids. Cp. page 99, lines 6-7, page 49, lines 13-23, and Fig. 4. These revisions are not believed to change the scope of the claims.

Respectfully submitted,

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Enclosure
-Deres (1989)

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